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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/126,096	07/30/98	THORSETT E	002010-137

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RAO, D	

ART UNIT	PAPER NUMBER
1624	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/126,096	Thorsett et al.
Examiner	**Group Art Unit**
Deepak Rao	1624

☒ Responsive to communication(s) filed on *Mar 1, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-18* is/are pending in the applicat

Of the above, claim(s) *5, 8, 9, and 11* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4, 6, 7, 10, and 12-18* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 5 & 10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 1-18 are pending in this application.

Election/Restriction

Applicant's election with traverse of Group III in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the restriction is improper as there is no serious burden on the examiner to search the entire scope of formulae I and Ia. This is not found persuasive because (as explained in the previous office action) the instantly claimed generic group of compounds represented by formula I or Ia, result in a myriad of compounds having an array of cyclic and non cyclic structures, e.g., in the instant claims when R^1 and R^2 together form a ring, the ring will contain N and $S(O_2)$ as the ring members, which is different from the ring formed by R^2 and R^3 together. These groups of compounds are diversely classified in classes 540-548 and various subclasses therein, depending on the substituent groups and accordingly, the groups of inventions presented in the previous office action are all distinct, each from the other because they have acquired separate status in the art, will support separate patents, and will require different fields of burdensome search for the respective inventions. Therefore, restriction for examination purposes, as indicated is considered proper. 37 CFR 1.141(a) provides that two or more independent and distinct inventions may not be claimed in one application. When a group of compounds are subject to the test of patentability, the whole molecule must be considered. One cannot classify and examine concepts based on bits and pieces of molecule, that is carved out of the whole

compound. The compounds of formula I or IA as instantly claimed do not form a single inventive concept within the meaning of 35 U.S.C. 121 because a reference that anticipates or renders obvious one of the groups would not necessarily render obvious another group and applicants have not clearly stated on the record that this is not the case..

The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of the species of Example 50 (page 115 of the specification) in paper no. 11 is acknowledged. This application has been examined to the extent readable on the elected invention, i.e., compounds of formula I or IA wherein **R^2 and R^3 together** with the nitrogen and carbon to which they are attached, **form a pyrrolidine ring**.

As per the restriction requirement of paper no. 6, Group III contained claims 1-2, 6-7 and 11-18. After careful review and reconsideration, **Group III** is amended to contain **claims 1-4, 6-7, 10 and 12-18**, which claims are under examination.

Claims 5, 8-9 and 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Rejections

Claims 1-4, 6-7, 10 and 12-18 are rejected on the grounds as being drawn to an Improper Markush Group(s). *In re Harnisch*, 206 USPQ 300. The claimed compounds and the methods that employ them present a variable core and, thus, the Markush groups represented by the terms

R^1, R^2, R^3 and R^4 having variably different definitions, render the claims clearly improper. It is considered that a Markush-type claim encompassing such species is directed to multiple independent and patentably distinct inventions when the species are so unrelated and diverse that a reference anticipating the claims with regard to one of the species will not render obvious under 35 U.S.C. 103(a) with respect to another member. Furthermore, in this regard, lack of a common nucleus or core is evidentiary of independent and distinct inventions and also from the variably diverse definitions of R^1-R^4. Each species can be considered to be patentably distinct from the other on the basis of its properties.

Deletion of non elected subject matter would obviate this rejection.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-7, 10, 12-13 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein R^2 and R^3 together with the nitrogen and the carbon to which they are attached form a pyrrolidine ring, does not reasonably provide enablement for all other compounds embraced by the instant claims reciting 'R^2 and R^3 together form a heterocyclic or substituted heterocyclic group'. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

1. The specification provides no sufficient enabling disclosure by way of representative examples or reasonable disclosure of starting material sources for the plethora of heterocyclic groups unsubstituted and substituted, permitted by the definition of R^2 and R^3 together which includes various monocyclic and fused hetero rings of various sizes (as per the definition in page 52, lines 24-29). Additionally preparation of only compounds wherein R^2 and R^3 together form a pyrrolidine (i.e., prolinyl) is taught and not the other heterocyclic groups embraced by the instant definition, see pages 55-64 in the specification and the examples. Such diverse embodiments have not been shown by adequate representation to be applicant's invention. Specification is silent about the availability of necessary reactants needed to prepare such a scope and does not particularly teach the means by which they may be prepared. See *Ex parte Moersch*, 104 USPQ 122; *In re Howarth*, 210 USPQ 689; *In re Lund*, 153 USPQ 625; *In re Wiggins*, supra.

2. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art (directed to VLA-4 binding activity) for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the

pharmaceutical art. The only elected compounds made (prolyl derivatives) are so different from the compounds embraced by the genus such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the compounds. Receptor activity is generally unpredictable and highly structure specific area.

In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the compounds commensurate in scope with the claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds as therapeutic agents for VLA-4 mediated conditions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-7, 10 and 12-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. The definition of "aryl" in the claims is of indefinite scope. In the specification (see page 45, lines 4-5), the term 'aryl' has been defined to be 'an unsaturated aromatic carbocyclic group...', however, the examples provided for condensed rings contain heterocyclic rings. See *In re Hill*, 73 USPQ 482 regarding distortion in art recognized terms. Clarification is required.

2. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, the claims recite the broad recitation "heterocyclic" (see the definitions of the variables R^1-R^6 and Z), and the claims also recite "heteroaryl" which is the narrower statement of the range/limitation. The specification on page 52, lines 24-29, defines heterocyclic to be both a saturated as well as an unsaturated group.

3. The claims 1-2 recite "A compound .... **and** pharmaceutically acceptable salt thereof..." which is confusing. It is not clear if a compound **or** its salt is claimed or a mixture of the compound and its salt is intended in each of these claims. Replacing "and" with --or-- is suggested.

4. In claim 2, the definitions of Y and Z are not in the alternative form. For example, Y is defined to be "hydrogen, alkyl, substituted alkyl, aryl **and** substituted aryl", which is unclear because it is not understood how Y can be all of the groups as defined. It is suggested that the term 'and' be replaced by -- or -- in both Y and Z definitions.

5. In claims 12-13, the symbol " Φ " is used in many of the groups and the claims also contain "phenyl" in many of the groups. First, there is no explanation provided for " Φ " and further, duel representation of the group is not permitted within a claim.

6. Claim 14 also recites "A compound .... and pharmaceutically acceptable salt thereof..." which is confusing. (See reason no. 3 above).

7. In claim 14, page 141, lines 31-35, the recitation starting from "as well as any of the ester...." to the end of the claim is confusing and unclear.

8. In claim 16, the structural formula (on page 142) shows a variable $R^{6'}$, however, there is no definition provided from this variable. A definition is provided for $R^{6'}$ on page 143. Consistent terminology through out the claims is required.

9. Regarding claim 18, the phrase "**including**" [all occurrences, e.g., "diabetes (including acute juvenile onset diabetes)" in lines 3-4, etc.] renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Also, line 9 contains the term "**such as**" which is not permitted.

10. Further, in claim 18, lines 6-7, it is not clear what is intended by "other cerebral traumas".

11. Furthermore, all of the diseases listed in claim 18 are **not** inflammatory diseases. It is not understood how 'Alzheimer's disease' is also recited under inflammatory disease.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

1. Claims 1-3, 6-7, 10, 12-13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 4,154,732 (cited in IDS) or the corresponding Chemical Abstract 117:211689 (cited in PTO-892). The reference teaches a group of prolinyl derivatives, see the formulae in the abstract. The instant compounds differ from the reference compounds by a $-CH_2$ group, i.e., in the instant case R^4 is methyl. One having ordinary skill in the art would have been

motivated to prepare the instantly claimed compounds because such structurally homologous compounds would have been obvious to the skilled chemist from the disclosure. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. *In re Haas*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950). *In re Dillon*, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990). Compounds wherein R^6 is alkoxy, i.e., the esters would have been obvious over the reference free acid compounds because the idea of modifying carboxyl groups of compounds to the corresponding esters is well within the expected ability of one skilled in the art. See *Ex parte Bergel et al.*, 121 USPQ 522 (POBA 1949); *In re Ward*, 329 F2d 1021, 141 USPQ 227 (CCPA 1964).

2. Claims 1-4, 6-7, 10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al., WO 96/22966 (cited in IDS). The reference teaches a generic group of compounds which embraces applicant's instantly claimed compounds. See formula (I) in page 14, wherein Y is SO_2, n is zero and R_2 and R_3 together with the atoms to which they are attached form a heterocycle. The compounds are taught to be useful as therapeutic agents for the treatment of inflammatory diseases, etc., see the abstract. The claims differ from the reference by a $-CH_2$ group, i.e., in the instant case R^4 is methyl. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar properties and therefore, the same use as taught for the genus of the reference compounds. It has been held that compounds that are

structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-7, 10 and 12-18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 (and other dependent claims) of copending Application No. 09/126,095. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is no patentable distinction. The instant compounds are homologs of the reference compounds, i.e., they differ by a $-CH_2$ group (in the instant claims R^4 is methyl). One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar properties and therefore, the same use as taught for the genus of the reference compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statements filed on March 30, 1999, June 21, 1999 and May 31, 2000 and copies are enclosed herewith. The references that were crossed off were either duplicate entries or were lacking a publication date. The cited U.S. Provisional applications are not available for 35 U.S.C. 102(e) rejection, as they are not disclosed in a prior art U.S. Patent. See MPEP §2127. All pending U.S. Applications are preserved in confidence, see MPEP §2127, paragraph IV.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Rao whose telephone number is (703) 305-1879. The fax phone number for this Group is (703) 308-4556. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

Mukund J. Shah
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Art Unit 1624

Deepak Rao
September 26, 2000